REMARKS/ARGUMENTS

Claims 1-33 have been cancelled. There is no change to the previously presented claim 34. Claims 35-51, which all depend from independent claim 34, are newly added. Specifically claims 35-49 are added to incorporate the limitations of previously presented independent claim 18 and its dependent claims 19-32, respectively. Support for new claims 50-51 can be found at page 4, paragraph 5 of the originally filed specification. No new matter is added. Moreover, for reasons expressed below, independent claim 34, which remains unchanged, is allowable. For at least the same reasons, new claims 35-51, which all depend from claim 34, are also allowable. The present amendments raise no new consideration or require new search. Therefore, entry of the above amendments after the final Office Action is respectfully requested.

Each of claims 18-32 is rejected under 35 U.S.C §102(b) or 35 U.S.C §103(a) as being anticipated by or obvious over Morris et al. (EP 0 830 858 A1) as evidenced by Nakajima et al. (U.S. 3,926,817). These rejections have now become moot, because claims 18-32 have been cancelled.

Rejection of claim 34 as being obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima.

Claim 34 is rejected as being obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. Applicants respectfully traverse.

Claim 34 recites a pharmaceutical formulation comprising a homogeneous mixture of: (a) **uncoated** olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof; (c) a polysaccharide and optionally; d) one or more additional excipients.

Morris teaches an olanzapine formulation in which the active ingredient olanzapine is

coated by a polymer. Morris repeatedly emphasizes the criticality of coating olanzapine with a suitable polymer in many paragraphs. *See*, for example, the abstract, page 2, lines 6-28 and 45-51, page 4, lines 45-57, and claim 1. Morris does not disclose a formulation comprising uncoated olanzapine.

At page 10, third paragraph of the Office Action, the Examiner argues that Morris implicitly suggests a formulation comprising uncoated olanzapine, because Morris teaches coated olanzapine only as a "preferred embodiment (*see* pg. 5, lines 5-51)." This is incorrect.

As noted above, Morris consistently discloses and emphasizes in the abstract, specification, and the claims the criticality of coating olanzapine with a suitable polymer. As to page 5, lines 50-51 identified by the Examiner, it states: "The solid formulation is most preferably prepared using hydroxypropyl methylcellulose coated olanzapine." This statement simply expresses that hydroxypropyl methylcellulose is a preferred polymer for coating olanzapine; it does not disclose that coated olanzapine, regardless of what specific polymer is used for the coating, is a preferred embodiment. Rather, as evident from the full text of Morris, coated olanzapine is a necessary and essential feature of the invention described therein.

Contrary to the Examiner's argument, Morris in fact contains many statements that would discourage or teach away a person of ordinary skill in the art from making an uncoated olanzapine formulation. For example, at page 2, lines 6-13, Morris discloses,

> "However, improved oral formulations were desired in light of the moisture sensitive, metastable nature of olanzapine, the tendency of olanzapine to undesirably discolor in the known tablet formulation, that is the formulation disclosed in 5,229,382, and due to the surprisingly potent nature of olanzapine. A pharmaceutically elegant granule or microparticle formulation was especially desired. Such granule formulation was particularly challenging in light of the exacerbating effect of surface contact with ambient air and moist environments and the relatively large surface area inherent in a granule formulation.

At page 2, lines 32-51, Morris discloses:

> Olanzapine, a potent compound showing promising activity for use in treating psychotic patients, tends to be metastable, undergo pharmaceutically undesired discoloration, and demands care to assure homogeniety of the finished solid formulation.
>
> Applicants have discovered that olanzapine undergoes undesirable discoloration when contacted with certain excipients including powder blends. Further, the discoloration is exacerbated by ambient air conditions, at elevated temperatures, and by moist environments.
>
> Although the discoloration phenomenon does not produce an increase in the number of total related substances, the browning and mottling appearance is not generally considered pharmaceutically acceptable for commercial purposes. Further, the discoloration is particularly disturbing when a tablet formulation is administered to a psychotic patient, which patient may be especially troubled by the changing appearance of their medication.
>
> The discoloration phenomenon is particularly troublesome for a granule formulation. Such formulation inherently exposes more olanzapine to ambient or humid conditions by virtue of the increased outer surface area relative to a solid tablet formulation. The present invention provides the desired pharmaceutically elegant granule formulation.
>
> Applicants have discovered that coating the olanzapine compound with a polymer selected from . . . as a coating or subcoating provides a uniform, physical stability and effectively prevents the undesired discoloration phenomenon in the formulation.

When reading the above disclosures, a person of ordinary skill in the art would not leave olanzapine uncoated, which would result in undesirable color change and appearance, in particular considering that the olanzapine formulation would be used for a patient suffering from lallucinations, delusions, and being out of touch with reality.

At page 10, third full paragraph of the Office Action, the Examiner also argues: "Morris et al. further teach that uncoated tablets stored at ambient conditions in amber, high density polyethylene bottles do not show signs of discoloration after 24 months unless that tablets are exposed to open air then discoloration occurs within 5 days (see pg. 4, lines 45-48). Thus it

would be within the skilled artisan to formulate the tablets as uncoated tablets if the intended use is for rapid usage of the formulation before the discoloration period and/or rapid dissolution." For reasons expressed below, the Examiner's argument lacks merit.

First, the statement quoted by the Examiner from page 4, lines 45-48 of Morris discloses that discoloration of uncoated olanzapine tablets occurs **within** (not after) 5 days after the tablets are exposed to open air. In other words, the color of the uncoated olanzapine tablets may occur any time but by no later than (not at least) 5 days after the tablets are exposed to the air. Because the discoloration may occur any time after the uncoated tablets are exposed to the air, one could not ascertain the discoloration period and would not intend rapid usage of uncoated olanzapine tablets before the discoloration period, as proposed by the Examiner.

Second, a person of ordinary skill in the art would not expect from the statement quoted by the Examiner from page 4, lines 45-48 of Morris that a formulation containing uncoated olanzapine, as described in claim 34 of the present application, would have a desirable stability for a substantial period of time. For example, as shown in Example 3, a formulation containing uncoated olanzapine in accordance with an embodiment of the present invention has been stable for at least 6 months under 40^0C/75 RH. As explained at page 3, last paragraph of the present application,

> It was surprisingly found by the present inventors that stable pharmaceutical formulations comprising olanzapine as the active ingredient, which do not show any undesired discoloration and have an excellent dose uniformity, can be prepared by a simple direct compression process if olanzapine or a pharmaceutically acceptable salt thereof is first homogeneously mixed with certain excipients and then subjected to direct compression. The direct compression is preferably performed in the absence of any solvent. In view of the fact that the excipients used by the present inventors are commonly used for manufacturing tablets, the finding that they allow the production of stable olanzapine formulations without any need for a coating or wet granulation was totally unexpected.

Indeed, according to the statement quoted by the Examiner from page 4, lines 45-48 of Morris, a person of ordinary skill in the art would expect that a formulation containing uncoated olanzapine would not be stable for more than 5 days under room temperature and 40% relative humidity. Therefore, the unexpected results of the present invention further demonstrate the non-obviousness of the invention described in claim 34.

Third, it is not clear from the statement quoted by the Examiner from page 4, lines 45-48 of Morris that the tablets discussed therein comprises uncoated olanzapine, because the term "uncoated tablets" likely means that tablets containing coated olanzapine and other excipients as a whole are not coated from the outside in a final step (e.g., enteric film coating and sugar coating).

Additionally, the Examiner states that the findings by WIPO do not necessarily bind on USPTO's examination of the counterpart application. *See* page 4, first paragraph. That being true, the underlying substantive reasons for WIPO's findings that the claims of the corresponding PCT application are novel and have an inventive step in view of the same prior art applied by the Examiner here, i.e., Morris et al., may be similarly applicable to the claims in the present application. For example, WIPO's specific discussion as to why the claims are novel and have an inventive step in view of Morris certainly sheds light on how a person of ordinary skill in the art would understand the differences between the present invention and the Morris, and whether the results of the present invention would be unexpected from Morris. The International Preliminary Examination Report should have been placed in the U.S. Patent Office's record of the present application. For the Examiner's convenience, Applicants enclosed herewith a copy of the relevant page of the International Preliminary Examination Report discussing the reasons why the claims are novel and have inventive step in view of Morris (Exhibit 1).

Based on the foregoing, claim 34 is not obvious over under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. Withdrawal of the rejection is respectfully requested. For at least the same reasons, claims 35-51, which all depend from claim 34, are also patentable in view of the art of record.

Accordingly, it is believed that the present application has been placed in condition of allowance. Early and favorable consideration is respectfully requested.

It is believed that no additional fees or charges are required at this time in connection with the present application. However, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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